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Channels of Communication: Extracellular Vesicles in Environmental Stress and Human Disease

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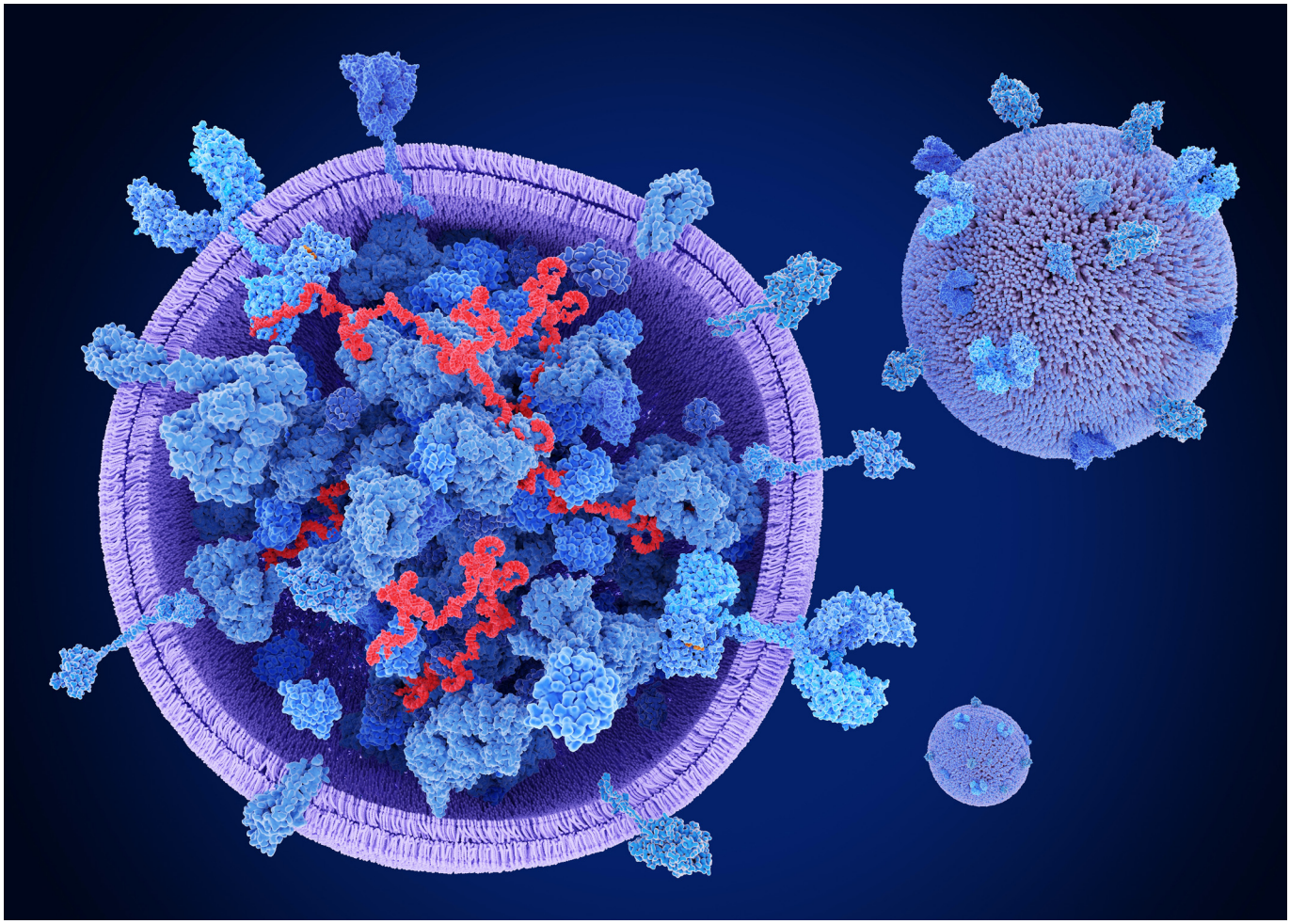
Extracellular vesicles (EVs) are small, membrane-bound structures released by cells as a means of communication.[1] They shuttle their "cargo"—lipids, proteins, nucleic acids, and other molecules—throughout the body via the bloodstream, influencing such physiological processes as immune responses and neuronal firing. As such, they play an important part in normal cellular physiology. Their involvement in mechanisms of cellular stress, early disease development, and environmental exposures means they can potentially serve as indicators of those processes. Since first imaged with electron microscopy in the 1960s,[2] EVs are now recognized for their potentially transformative diagnostic and therapeutic uses in numerous fields. So say the authors of the first *Environmental Health Perspectives* Seminar.[1] The Seminar article type was established to promote interdisciplinary exchange and knowledge by providing state-of-the-art information on emerging research directions, important methods, and underlying scientific principles.

In theory, EVs could represent a breakthrough in biomedical science: a tool through which researchers could assess whole-body exposures and health via a single blood draw, or liquid biopsy. "I am extremely excited about the prospect of extracellular vesicles as biomarkers for disease, exposures, and more," says Ian White, a professor of bioengineering at the University of Maryland who was not involved with the Seminar. "There seems to be a lot of great potential, 'potential' being the key word."

Recent research has shown that EVs may mediate the effects of exposure to environmental stressors.[3–6] But exactly how this works, and how such knowledge could be used to monitor and assess health effects of pollutant exposures, is largely unknown and a subject of increasing interest.

Senior author Daniel Shaughnessy, a health scientist administrator at the National Institute of Environmental Health Sciences, agrees that research on EVs holds great promise, yet has a long



This illustrated cross-section of an exosome—one type of extracellular vesicle—reveals its cargo of proteins (blue) and messenger ribonucleic acid (red). Extracellular vesicles "play key roles in intercellular communication, in both normal cell physiology and in disease processes, including immune suppression, inflammation, and oncogenic signaling" wrote the authors of the new Seminar. Image: © Juan Gaertner/Science Photo Library.

way to go. "There are still lots of open questions," he says. "There are the mechanics of how EVs are produced; what is the biogenesis? How was cargo selected from the donor cell? How are they recognized by the recipient cells?"

The coming years could bring major advances. "The whole field of extracellular vesicles in health and disease is really hot right now," Shaughnessy says, noting the Seminar authors' hopes of stimulating new research in the field.

Emerging evidence suggests EVs may be involved in the development of neurodegenerative conditions—including Alzheimer's disease,[7] Parkinson's disease,[8] and amyotrophic lateral sclerosis,[9] all of which have environmental risk factors, including exposures to viral particles,[10] heavy metals,[11] tobacco smoke,[12] and air pollutants, such as particulate matter.[13] "EVs offer a promising gateway into understanding, treating, and possibly delaying neurodegenerative disorders," the authors wrote. But "there is still a vast uncharted territory to navigate."

In the respiratory system, EVs appear to mediate inflammatory effects of pollutant exposures.[14] In one study, rats exposed to tobacco smoke showed changes in blood EV biomarkers that were associated with lung function decline.[15] In another, smokers with preclinical loss of lung function had a higher circulating level of a type of EV called endothelial microparticles, known to be elevated in vascular-related disorders,[16] than did smokers with normal lung function. Both groups had more endothelial microparticles than healthy nonsmokers.[17]

In reproductive health, studies suggest that exosomes (another type of EV[2]) from fetal and maternal tissue can activate labor, potentially causing preterm birth.[18,19] In this role, exosomes also may mediate the relationship between some environmental exposures—including cigarette smoke, certain flame retardants, and bisphenols A and S—and premature labor and preterm birth.[20–22]

To realize the promise of EVs, researchers need standardized methods and breakthroughs in the technical limitations around efficiency and throughput in human biofluid assays. Scientists must find ways to handle intraindividual variability in EVs driven by infection, diet, medication use, and other factors that are difficult to control in population studies, the Seminar authors wrote.

Organ-on-a-chip experimental models, or microphysiological systems, also hold promise for complementing EV findings from population-based studies, they wrote. These platforms overcome some of the shortcomings of animal models and traditional *in vitro* cellular models by mimicking the structure and function of human organ systems.

"As with any new field, it's going to take a fair amount of fine-tuning of the methods," says first author Vrinda Kalia, an associate research scientist at Columbia University. "What I imagine would be really helpful is a controlled prospective study that focuses specifically on EVs and environmental exposures."

The Seminar represents an important translation of recent advances in studying this emerging mechanism of toxicity, says Julia Rager, an assistant professor of environmental sciences and engineering at the University of North Carolina at Chapel Hill, who was not involved in the Seminar. "Studying this mechanism relies upon specialized molecular biology–based methods that can sometimes be difficult to translate into the field of public health and environmental research," she says. "Papers such as this are key to bridging these fields of study."

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